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13. ABSTRACT *(Maximum 200 words)*

The Phase I program carefully identified and defined the problem of noninvasive sensing of deep tissue oxygenation. Existing technology was assessed in light of the requirements needed to meet the Army objectives for a sensor system that integrates into a much larger effort to equip the foot soldier of the future with advanced protective capabilities. An approach based on diffuse reflectance tomographic imaging was identified as having the potential to meet the objectives of the sensor development initiative being sponsored by the U.S. Army.

Diffusive tomography in the context of this application would generate an image of the absorption characteristics of the irradiated skeletal muscle. When the imaging wavelength is matched to the absorption of hemoglobin and myoglobin the resulting image would reflect the state of oxygenation in the tissue. The power of the method is the ability to process the detected light signal to determine the spatial origin thus surface and deep tissue information can potentially be resolved. A program for developing this approach was proposed to the U.S. Army sponsor.

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Kim Voss 10-27-95

PI - Signature Date

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1.0 INTRODUCTION

As U.S. Army commanders plan for future actions, their forecasts recognize that evolving geopolitical circumstances and advancing technology will continue to alter and redefine the combat force mission. Making reliable predictions of future trends in military engagements has the important purpose of allowing the planners to identify technological advances needed to maintain maximum effectiveness of combat forces. One area in which the Army is pursuing a significant advance in capabilities is in the personal battle gear for the foot soldier of the future. Going under the banner of the Twenty-first Century Warrior (TFCW), a system of weapons, sensors, heads up display, communications, ground navigation, protective devices and soldier computer forms an integrated protective system under development now and anticipated for the early twenty-first century. At this point the subsystems are at different stages of development ranging from operational stand alone technologies (e.g. global positioning systems) to early concept definition and feasibility demonstration projects. Within the latter category, the Army Medical Research and Materiel Command is pursuing development of physiologic sensors to enhance casualty care. Integration of physiologic sensors into the coordinated system of the TFCW is highly consistent with a focus on far forward care for improving outcomes for battlefield casualties.

There are several factors that support development of personal physiologic sensors for use in the integrated protective system. Statistics[1] on the incidence and outcome of wartime casualties show that in the Civil War and World War I more casualties died in hospitals and aid stations than on the battlefield. The opposite holds true in World War II (WW II) and continuing through Korea and Vietnam, which is attributed to the increasing sophistication of medical care at military treatment centers. With modern transport and treatment capabilities, only a very small fraction of wound victims transported off the battlefield to some level of treatment facility are not saved. However, the same statistics show that the rate of wounded in action remained the same through WW II, Korea and Vietnam. A significant fraction of these wounded had suffered penetration wounds and/or blast trauma with severe hemorrhage. The area of combat casualty care is faced with the difficult problem of improving treatment response and lowering the death rate for battlefield casualties.

To improve the future survival rate for these same kinds of casualties the means must be developed for applying almost immediate life sustaining measures in the far forward area. The far forward emphasis here meaning at locations even before the first level evacuation station where the field medic is the principal resource. The situation is complicated because the medical corpsman who will be called on to administer critical life sustaining measures generally has the least amount of formal medical training within the medical care delivery system. Providing timely, straightforward assistance in diagnosis and treatment options would enhance the ability of the medic to act effectively on behalf of the wounded during a very critical period.

While the future of armed conflicts will result in casualties of the blast and penetration type already mentioned, additional factors further increase the importance of far forward treatment. Military strategists suggest that future circumstances and technology could call for more highly dispersed troop deployment scenarios than past actions.[1] This dispersal detracts from effective military operations if individual soldiers become isolated from support and

commanders lose awareness of the status of their troops and the battle. The problem of identifying wounded and getting help to them becomes greater as they are more spread out. The TFCW concept counters the anticipated problem with the system of health status sensors, location devices and communication link.

Blast and penetration wounds are not the only threat faced by the future soldier. Past experience has shown that the extreme physical and psychological stress of battle account for significant battlefield casualties and disabilities. The simple factor of greater troop dispersal may contribute to additional stress since the soldier with a sense of isolation in the face of deadly threat will likely experience greater stress than when he is in a group. Adding to the real and perceived threat will be a trend for more nighttime action made possible by night vision systems. Also, the soldier may come under the threat of chemical, biological and directed energy weapons. A countermeasure to these exotic weapons threats could involve additional protective wear adding further to the body burden of required equipment. All of these factors contribute to the overall physical and psychological stress bearing on the soldier. A means to monitor the physiological response to stresses in real time makes it possible to direct preventive measures before the soldier becomes seriously compromised or incapacitated.

The concept for physiologic sensors that function as part of the continuously worn gear of the combat soldier has then the two aspects of usage. In the capacity of a continuous or semicontinuous monitor the sensor system could detect signs of potentially disabling fatigue and stress. A warning could be issued prompting the soldier to initiate preventative measures. Similarly, commanders could be appraised of the current condition of troops that could influence the ability to carry out certain missions. Then in the acute situation where a soldier is down in the field the physiologic sensor system could supply vital information for treatment. First by detecting the down or incapacitated condition and issuing a call for help. Once the field medic can initiate aid, the sensor system could provide feedback about whether the victim is responding in the desired way. In either capacity, an important capability of the measurement system is the ability to collect baseline readings on the healthy, uncompromised individual as a reference point.

The Army's general concept of a physiologic sensor system has been introduced thus far without mention of the actual physiologic parameters of interest. Identifying the parameters that will be most useful is part of the overall development process. Progress will come by an iterative process driven by knowledge of human physiology and developments in sensor technology. One element that will be common to any sensor is noninvasive operation. A single universal sensor is probably not realistic so currently the concept presumes sensing of different parameters by distinct sensor elements. Under the general solicitation that led to funding on this project, the Army had identified blood flow, pH and tissue oxygenation as three key areas of interest for sensor development.

This report covers a Phase I Small Business Innovative Research effort on Tissue Oxygenation Measurement System approaches. The overall goal was to identify an approach for sensor development that could address the criteria of making measurements noninvasively, of sensing in deep tissue regions and of generating output that accurately reflects deficiencies in tissue oxygenation. The program had three major tasks that define the objectives. First, to

identify and assess oximeter device approaches for applicability and potential to be made compact and rugged, second to identify a sensor approach that had potential to meet Army objectives and third to plan the research and development required to demonstrate the approach during a Phase II program. These objectives were met, leading to a recommendation for continued development of a near infrared (NIR), tissue oxygenation, imaging sensor.

2.0. RESULTS OF THE PHASE I WORK

The purpose of the Phase I program was to identify science and technology applicable to making noninvasive tissue oxygenation measurements. Once identified, this information could be assessed to determine whether an existing, new or hybrid approach had merit for the Army need. Underlying this assessment phase was a definite emphasis toward device concepts even though device fabrication was not forecast until Phase II.

Going into the Phase I program it was known that oximeter instruments were commercially available and that some types were well established in medical practice. Furthermore, *in vivo*, noninvasive sensing of oxygenation was identified as an active area of research both to improve diagnostic tools and provide basic physiological information. It was not apparent that any of the commercial oximeters or laboratory instruments were adaptable to the on-the-soldier package. The plan called for assessing existing oximetry methods to determine if engineering modification to harden and miniaturize would meet requirements or whether a basically new design approach was required. Experimental methods were also examined. An important aspect of the assessment was to define what parameter the methods actually measure; the Army has defined their need as a measure of deep tissue oxygenation.

The Phase I results section summarizes some important aspects of tissue oxygenation which contribute background support for the conclusion that several existing oximetry approaches are unsuited for this application. The assessment of existing technology led to identification of diffuse reflectance imaging as having potential to provide a direct indicator of oxygenation in skeletal muscle tissues. A model simulation of tissue scattering and absorption for two states of oxygenation was used to demonstrate image reconstruction that accurately detects the change in oxygen saturation. A proposed Phase II program would pursue the experimental development to demonstrate this approach in a laboratory prototype.

2.1 Technical Objectives - The overall objective of this program was to produce a compact, noninvasive sensor system for determining the state of oxygenation of surface and deep tissue. The sensor system must be portable to the extent that it is worn by soldiers in the field for extended periods. In addition to the rather stringent DoD application, there are civilian applications in trauma care and diagnostic monitoring. Specific objectives listed below, were directed at assessment of existing noninvasive oximetry devices and methods.

The Phase I technical objectives were to:

1. Determine whether commercial off-the-shelf oximeter equipment can be adapted to the needs of deep tissue oxygenation monitoring.

2. Identify and pursue methods based on alternate chromophores to hemoglobin.

3. Determine whether photo-acoustic spectroscopy can be used to measure PO_2 in possible conjunction with Doppler ultrasound measurement of flow and/or photoacoustic spectroscopy measurement of pH.

4. Determine whether NMR has any practical applicability to tissue oxygenation measurement.

5. Select the best approach for tissue oxygenation measurement and incorporate it into a plan for prototype demonstration and testing during phase II.

2.2 Device Requirements and Use - The goal of the Phase I program was to identify an approach that would lead to a practical sensor device so considerable importance was given to defining target requirements to focus effort toward development issues. The sensor concept should be compatible with design strategies that can meet the following basic criteria.

1. Noninvasive, personal sensor system.
2. Compatible with physical activity under extremes of battlefield environment.
3. Output correlated to tissue oxygenation values with true diagnostic value.
4. Adaptable to wireless input/output.

An important aspect of the first design criterion is universal applicability. The user population will vary in body build, relative lean to fat tissue mass, skin pigmentation and physiologic features such as hematocrit and both pulmonary and circulatory capacity. The sensor must be readily calibrated to account for these variabilities. The first and second criteria of portability and function on an active subject imply not only ruggedness but a system that will not interfere with necessary duties and activity.

The third requirement defined above embodies the qualities of low susceptibility to interference while producing a response to a physiological change that has definite significance to the degree of health or distress. The latter presumes that the physiologic response to wound trauma and battlefield fatigue is well defined under all the possible situations that could arise which is unlikely to be the case. However, in the assessment of available sensor technology the documented interferences and application reports can be judged as to how severe the problem would be if use were projected to active subjects in an uncontrolled environment. The emphasis put on developing a deep tissue sensor emphasizes the goal of making the output have firm diagnostic value under the presumed conditions. The deep tissue measure is in contrast to surface oxygenation values which have a higher likelihood of interference from less significant physiologic changes.

The fourth criterion, wireless capability, anticipates integration into the larger initiative to equip the future soldier (i.e. the Twenty-first Century Warrior) with a suite of other battlefield sensors and displays. Within this concept a common computer module serving all the sensors

is linked by wireless control and data transmission. The specific communications link is outside the immediate scope of the oxygenation sensor program, however, it must be anticipated in the development strategy.

2.3 Background Concepts - The discussion of sensors that respond to physiologic oxygen levels is based on an understanding of the processes responsible for oxygen transport in the body. A short explanation of pertinent topics introduces the assessment of available sensor technology. In addition to oxygen transport in tissue, it is important to appreciate the basic optical characteristics of tissue in order to understand the operating principles and difficulties of noninvasive oxygenation sensor systems.

2.3.1 Oxygen Transport - The basis of cellular metabolism is the enzymatic action to reduce dioxygen (O_2) which drives the formation of important high energy cellular biochemicals. A cell deprived of a continuous resupply of O_2 cannot function; if conditions exist that sustain an O_2 deficit and this prevails on a macroscopic scale organ failure then death can result. Because of the life sustaining dependence on available O_2, tissue oxygenation (i.e. the site of use) is a valuable diagnostic parameter. The constraint of noninvasive monitoring gives rise to the question of which tissue is most appropriate to getting good diagnostic information. The answer cannot be given unambiguously because it will depend on the reason for monitoring and possibly what is possible with the sensor device itself. However, it can be concluded that muscle tissue is one logical choice. Muscle tissue constitutes a significant fraction of body mass and is distributed over the whole frame relatively accessible beneath the skin. A sophisticated circulatory system has evolved to accommodate the significantly different O_2 demands of resting and exercising muscle. A sensor system monitoring muscle tissue oxygenation must function under both of these normal conditions (rest and exercise) as well as trauma induced abnormal states.

Oxygen is supplied by the action of breathing air which normally contains 21% O_2. The lungs and active circulatory system (heart and blood vessels) capture and then convectively transport the O_2 to all regions of the body for uptake by the tissues. Within the lung, inspired O_2 in the gaseous state diffuses across capillary membranes where it is bound in a complex by the hemoglobin (Hb) in the red blood cells. Formation of the hemoglobin-oxygen complex (Hb-O_2) is strongly favored and only a small fraction of the inspired O_2 is taken up in each breath cycle so the hemoglobin binding capacity is very close to 100% saturation in freshly oxygenated blood and the O_2 partial pressure or tension is very nearly that of the inspired air. Freshly oxygenated blood is taken into the heart and pumped out through the series of successively branching arteries and arterioles to the capillaries. In the Krogh[2] model of O_2 transport blood arrives at the arteriolar end of the capillary at its fully saturated value. As oxygenated red blood cells pass down the capillary the Hb-O_2 complex will dissociate as it passes tissue with a lower O_2 tension. The blood emerges from the capillaries into the venous network still partially oxygenated but at a lower O_2 tension than arterial blood. The venous blood cycles back to the lungs for reoxygenation. Figure 1 depicts the cascade of O_2 tension by the process just described. As tissues take up O_2 from the blood, there is a corresponding drop in the fractional saturation of the O_2 binding capacity of hemoglobin often represented by SxO_2 with x denoting vessel type. Thus SaO_2, arterial saturation is greater than SvO_2, venous saturation and the capillary values are variable between the inflow and outflow sides.

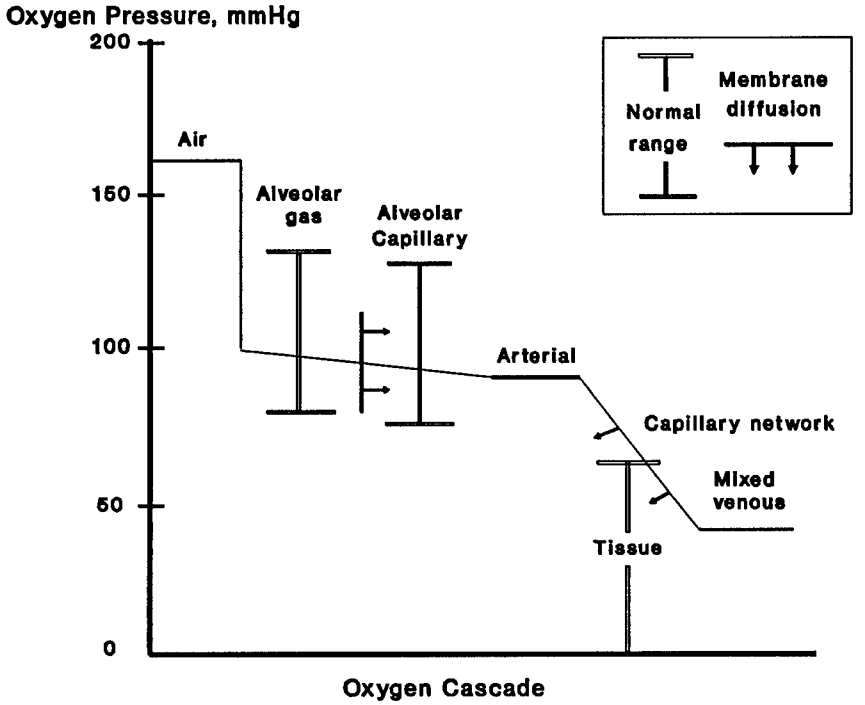

Figure 1. The oxygen pressure cascade going from inspired air to tissue.

The importance of blood oxygenation to this discussion is that SaO_2 is the principal parameter measured by some commercial oximeters. The inference is made that blood oxygenation reflects tissue oxygenation which will be addressed later in this discussion. If blood saturation is accepted as the appropriate parameter for monitoring oxygenation, consideration of the oxygen cascade, figure 1, points out that the fractional mix of blood type (i.e. arterial, capillary and venous) must be known. This in turn implies that the tissue volume sampled by the sensor is known and the blood mix does not change. Pittman in a review of current research on oxygen exchange in skeletal muscle[2] points out that the oxygen cascade picture of figure 1 is erroneously simple, particularly for muscle at rest. Diffusion of O_2 from both arterioles and venules into surrounding tissues and back into vessels was shown (*in vivo* hamster studies) to be a significant factor causing considerable variability in SaO_2 in vessels and capillaries. Modeling suggested that during exercise with higher blood flow the heterogeneity of saturation caused by diffusion would be lessened but this has not been experimentally verified. These results suggest the potentially degraded value of blood oxygenation data if an ill defined or too small tissue volume is sampled.

The next stage in tissue oxygenation after convective transport to the capillary beds, occurs by diffusion of O_2 released from the Hb-O_2 complex across the cell membrane. Once in the cell O_2 diffuses to the sites of active consumption, principally the mitochondria. Muscle tissue also contains myoglobin (Mb), another O_2 binding protein similar to the hemoglobin in blood. Myoglobin may play some part in transport but also acts as an intracellular store of O_2.

Since muscle tissue was identified above as a potentially important site for monitoring oxygenation there are two important aspects of myoglobin that must be taken into account. Hemoglobin and myoglobin have essentially the same chromophore and thus are spectrally indistinguishable at the wavelengths utilized in NIR based spectral oximeters. More is said below on the spectral properties of these oxygen carrying proteins. It is known that Mb binds O_2 more strongly than Hb; the 50% dissociated partial pressure for Hb is about 30 mmHg but just 2.5 mmHg for Mb. Thus under the assumption of oxygen tensions presented in figure 1, Mb is expected to stay essentially fully oxygenated under normal conditions at rest. Ischemic episodes will reduce oxygen levels to where Mb becomes deoxygenated in all individuals but exercise may or may not cause some desaturation of Mb-O_2 to Mb[3].

2.3.2 Physiologic States of Tissue Oxygenation - Several different conditions of physiologic O_2 deficit can result. Ideally a sensor should have the capability to differentiate these states which are defined here.

Healthy individual - For the healthy individual breathing good air tissue oxygenation is maintained by adequate pulmonary and circulatory function. Even under the stress of exercise normal feedback mechanisms respond to increased demand and limit activity to supply capacity. Of course situationally induced conditions can lead an individual to physically exert beyond the warning signs of normal fatigue and cause some of the dangerous deficit conditions described next.

Ischemia - Ischemic conditions refer to severe reduction or shutoff of blood flow to a region.

Hypoxemia - A hypoxemic condition indicates that the blood O_2 saturation is deficient or lower than the statistical norm (see figure 1).

Hypoxia - Hypoxia indicates the state of insufficient tissue oxygenation whether caused by ischemia, hypoxemia or some specific cellular disturbances.

2.3.3 Tissue Spectral Properties - Sensors that will probe subsurface tissue can be either passive or active. For the passive device to operate the sample must give off or radiate some entity that the sensor can detect as it emerges at the surface. A transcutaneous oximeter is discussed below that senses oxygen that diffuses to the skin surface from tissues and vessels below the skin. The active sensors produce a signal that is altered in a defined way by interaction with the sample and detected in the altered form. Oxygenation has been sensed by NMR and visible-NIR spectroscopic methods. The latter are the most important in terms of existing oximeter devices and proposed new approaches. The optical character of tissue, described briefly here, presents a challenge to making useful spectroscopic measurements with small, field practical devices.

The spectral region of interest for NIR oximetry methods as well as other photodynamic medical procedures runs from 600 nm at the red end of the visible to 1300 nm in the NIR. This band is frequently referred to as the "therapeutic window" based on the ability of these photons to penetrate tissue to significant depths. Beyond 1300 nm the water in tissue absorbs very strongly setting a long wavelength cutoff. Short wavelength ultraviolet (UV) photons below 300 nm are stopped in the epidermis by strong absorption by nucleic acid structures of the proteins. Melanin, the pigment in skin plays an important role in limiting penetration of UV-A (350 - 400 nm) photons below the dermis. The optical density spectrum of the melanin layer shows a uniform drop from the long UV through the visible to insignificant levels in the NIR. Hemoglobin and myoglobin, already mentioned for their role in oxygen transport are among a very few endogenous tissue chromophores in the visible and NIR range.

Most spectroscopically determined oximetry values depend on the difference in absorption strength of the respective oxy (Hb-O_2) and deoxy (Hb) forms of hemoglobin. Both forms exhibit strong absorption bands at wavelengths below 600 nm but these bands are not useful for *in vivo* measurements of thick tissue sections because of the overall high attenuation. Above 600 nm in the relatively transparent region, the deoxy form, Hb, has a weak absorption peak at 660 nm that is much weaker in the oxy form Hb-O_2. Changes in absorbance at 660 nm serve to track the relative ratio of Hb to Hb-O_2 forms which is referred to as the blood oxygen saturation, S. Additionally the absorption spectrum of hemoglobin shows an isobestic point (equal molar extinction for both forms) in the 815- to 820 nm range[4]; at a longer wavelength the oxy form is slightly more strongly absorbing. Generally, oximetry methods have used multiple wavelengths because interfering effects can be discriminated against.

It is important to appreciate that myoglobin exhibits virtually the same absorption spectrum as Hb across this working region. There is no way to use measurements at multiple wavelengths to resolve the absorptive contribution of a mixture of these two species as they exist in normally perfused muscle tissue.[4] As a result spectroscopic measurements that do indeed sample deep muscle tissue will return a composite signal of the two. For these measurements it is essential to incorporate this basis into the interpretation of the oxygenation value. In the discussion of oxygen transport, the point was made that Mb binds oxygen much more strongly than Hb. During short term blood desaturation caused by exertion, tissues may maintain a fully oxygenated Mb status posing no apparent threat to health. On the other hand, significant deoxygenation of Mb stores would indicate potentially serious hypoxia. One can then state that the most useful oxygenation measurement will be able to differentiate these states. Generally, the species resolution problem must be approached so that a calibration point is determined where blood saturation is minimal but myoglobin is fully oxygenated. Then the sensor would need to respond to the further change that occurs if Mb-O_2 is depleted. Obviously, sensors that do not generate a composite Mb + Hb signal cannot directly detect tissue hypoxia.

Apart from the coincidence of absorption features of the target analytes Hb and Mb, *in vivo* tissue absorption measurements are complicated by the highly scattering nature of tissue. Absolute scattering coefficients are at least 10 to 100 times greater than absorption coefficients. In effect, the scattering removes the directional information of the source beam and generates a distribution of path lengths for photons reaching any fixed detector location. With path length

uncertain, the unknown concentration of absorbers cannot be determined by the usual application of a Beer's Law expression. Alternatively, one can measure attenuation with a continuous source and apply Beer's Law with the result that the sampled volume element (i.e. the region containing photon paths) is unsure. The value of the measurement then depends on the strength of the correlation of the determined oxygenation value to the true tissue levels under all conditions of interest.

The scattering observed in tissues is anisotropic with a strong bias to forward scatter. The effective transport scattering coefficient incorporating the angular dependence of scattering is considerably smaller than the absolute value. Although scattering remains a highly probable event as the photon propagates into tissue the anisotropy is such that a higher fraction of the incident photons penetrate deeply compared to a situation of isotropic scattering. Relatively speaking this is good because measuring the state of deep tissue oxygenation requires getting the probe photons into the volume of interest. The possibility of making thick tissue measurements has been demonstrated by *in vivo* transillumination experiments on cat brain and dog heart[5], human breast[6] and human infant brain[7]. A similar measurement on human muscle[4] used detection of the back scatter signal since bones are much less transmissive than the soft tissues.

Although the examples above demonstrate the basic feasibility of deep tissue spectroscopy, thus far the available oximeter technology based on NIR spectroscopy appears limited to approaches that probe either the surface or peripheral circulation. These may serve very well in a clinical setting but have limitations for field use. An assessment of available oximeter sensors is presented now in view of the background of oxygen transport and tissue optical characteristics just discussed. Some commercial and experimental approaches operate on different principles than NIR spectroscopy and those are brought out in the section on that sensor. All of the identified approaches are looked at from the perspective of whether they would be suited for adaptation to a small, rugged field device.

2.4 Assessment of Methods for Noninvasive *In Vivo* Determination of Oxygenation - The importance of detecting abnormal tissue oxygenation has been stated. For patients under medical supervision in a modern hospital or clinic various invasive methods including drawing blood or insertion of catheters and probes are available for detecting oxygenation. This will remain the case. However, invasive methods are not always appropriate or practical even in the controlled clinical setting. As a result, the need for remote or noninvasive sensing methods has been met to a degree by commercially available instruments. Instruments that were identified include the pulse oximeter, a cerebral oximeter (optical, non-pulse) and a cutaneous oximeter. Laboratory methods that are presented cover photoacoustic spectroscopy, NMR, and NIR absorbance measurements.

2.4.1 Pulse Oximeters - Exploiting the spectroscopic properties of the hemoglobin system in a practical, noninvasive method to determine blood oxygenation is a difficult problem for reasons already brought forth. The various pulse oximeters on the market are all based on a similar approach to handling the measurement problem. This approach has some very definite advantages while also posing some limitations. An important quality of the pulse oximeters is their truly noninvasive operation. Not only does the sensor probe fit externally on a digit or

earlobe, but there is no need for external calibration by independent methods that are invasive. The nature of the sensor response allows some fundamental sources of variability to be normalized out. Thus the same sensor works on the different digits of the hand and on the hands of any of the potential user population without resort to individualized calibration factors. The self calibrating approach is a very desirable feature but must be interpreted cautiously based on the use in hospitals. An undocumented calibration process can take place when an invasive procedure is used initially to establish an accepted level and then the pulse oximeter is used to monitor changes. In this situation the clinician can ignore deviations in absolute accuracy if experience shows that trends in blood oxygenation are tracked.

The nearly universal applicability and turnkey type measurement capability of pulse oximeters are features that would be very valuable in an oxygenation sensor for the current application. However, pulse oximeters also have characteristics that preclude their adaptation for the proposed personal, field sensor. Some of these limitations entail sensitivity to interfering conditions but others deal with more fundamental aspects of the approach. Five aspects of clinical pulse oximeters impact their adaptability to meet current objectives; they are listed and then discussed here.

1. Dependence on pulsatile blood flow.
2. Attachment points restricted to extremities.
3. Inference about tissue hypoxia from arterial saturation.
4. Environmental and operational interferences.
   - Motion interference
   - Ambient light variations (room lighting)
   - Optical shunting across skin surface
   - Skin pigmentation
   - Temperature
   - Specific toxic hemoglobinemia
5. Fixed empirical calibration.

The first three points deal with basic issues regarding the measurement approach used for commercial pulse oximeters and are discussed in the following paragraphs. The environmental interferences given in the fourth point describe the types of conditions that have been reported to interfere with accurate readings in clinical usage. Examination of these operational interferences suggests that several would be very difficult to control in a field situation particularly on an active subject. The fifth point calls to attention that fixed computational factors are incorporated into the signal processing algorithms used by different instrument makers to correct for the spectral interference of carbon monoxyhemoglobin in the blood[8]. An average level is assumed which becomes a source of error whenever specific conditions cause a change from the assumed norm. The problem of spectral interferences presents itself to any of the methods based on NIR absorption of hemoglobin.

From the standpoint of the clinical instrument developer, the first two factors are not limits at all but represent sound strategies to this difficult measurement problem. The pulsed flow dependence stems from a signal algorithm that uses the change in hemoglobin absorbance (higher Hb/Hb-O_2 ratio) in capillary blood as oxygen tension drops due to uptake by the tissues. A portion of the monitored blood volume is recharged with fresh arterial blood with each heartbeat generating an oscillating component to the signal. There is also a component of constant attenuation from nonpulsatile factors. The absolute magnitude of both the oscillating (ac) and constant (dc) intensity losses depends on specific extinction coefficients that would be different for different individuals. However, using the ratio of ac to dc levels normalizes out the variation resulting in a population independent correlation of instrument signal to oxygen saturation. Pulse oximeters typically measure the ac/dc ratio at two wavelengths and then ratio these for improved signal discrimination. Typical wavelengths are in the red, 660 nm, where Hb absorbs more strongly than Hb-O_2 and in the NIR, 920 to 940 nm where the opposite relative absorptivity is the case. The ratio of oppositely oscillating signals forms the composite signal with a frequency that matches the heart rate.

The pulsed flow based measurement removes the individual variability in effective optical density. The other major aspect of the measurement problem is getting sufficient light intensity at the detector. While a transparent window for soft tissues was described above, the human body effectively attenuates light all across this window. Soft tissue is highly turbid because of light scattering qualities and most areas of the body have central bone structures that are highly opaque. The laboratory spectroscopist has available high intensity sources and ultra sensitive detectors to handle the detection limit problem; generally the sample can also be adjusted to match the power levels. These are not viable solutions for a practical oximeter. Instead, pulse oximeters use a sensor with light emitting diode (LED) sources that have sufficient intensity to transilluminate the fingertips or earlobes. These are relatively thin points on the body without bone so sufficient signal intensity is transmitted for detection by semiconductor detectors.

Considering the objective of a field usable sensor the operating characteristics of pulse oximeters appear to limit the applicability for a field soldier. Clearly the fingers cannot be encumbered with a sensor device and the earlobe may be equally impractical. It is apparent that the device does not function in the absence of pulsed flow. However, in an active battlefield situation the possibility is very real that pulsed flow could be seriously weakened or shutdown in the local vicinity of the sensor by wounds or other stresses. The effect of temperature fluctuations on the peripheral circulation would be particularly likely to cause interference. The critical dependence on pulsatile flow in the extremities (i.e. fingertip) would not be addressed by engineering approaches that simply miniaturize the overall device.

The third point in the list of pulse oximeter attributes deals with the fact that the pulse oximeter measurement yields a value for arterial saturation, SaO_2. Reliance on blood saturation may in fact not yield information on tissue oxygen tension. This is illustrated by considering the value of an indirect measure of tissue PO_2 by oximetry under four conditions that could theoretically prevail.

1. High arterial PO_2 and high tissue PO_2. If this condition holds then oximetry will suffice although this case is almost trivial since it implies no problem with oxygenation.

2. Low arterial PO_2 and high tissue PO_2. This scenario could be found in pathological states where gases or other biochemical agents either depress respiration or competitively displace oxygen from the hemoglobin binding site. Tissue myoglobin oxygenation could be adequate temporarily and maintain cardiac (but probably not brain) function. Oximetry alone would not provide correct information here and would be misleading if used for triage.

3. High arterial PO_2 and low tissue PO_2. This situation could arise in cases of extreme fatigue with pH changes in musculature or from metabolic poisons affecting myoglobin or oxygen diffusion in tissue. A direct measure of tissue oxygenation only would suffice here.

4. Low arterial and low tissue PO_2. This could be the most critical condition to detect and it could be crucial to differentiate from condition 2. In triage for instance it should be possible to grade casualties using an index derived from the measurement. For instance, the recent Japanese incident involving exposure to Sarin is an occasion where immediate evaluation of casualties would enable most of the resuscitative facilities to be deployed to most advantage. Oximetry based on arterial saturation alone will not be able to detect this state.

A measurement that involves a parameter directly indicative of tissue oxygenation would improve upon the inferred value that one gets from a pulse oximeter.

2.4.2 Cerebral Oximeter - A cerebral oximeter has become available (Somanetics Invos system) in the last several years that generates a measure of regional oxygen saturation by NIR spectroscopy of the cerebral microvasculature. Saturation values are based on the absorbance losses due to hemoglobin in the circulating blood. The algorithm uses an expected mix of arterial (25%), venous (70%) and capillary (5%) blood volume to set the baseline oxy/deoxy ratio. The system is not dependent on pulsatile flow like the pulse oximeter, so monitoring is possible during cardiac surgical procedures with the patient on circulatory bypass. The device is also expected to continue to monitor cerebral oxygenation under conditions of circulatory failure.

The basic principle supporting the function of the cerebral oxygenation monitor has been presented in the background sections. In a published study on the utility of the Somanetics cerebral oxygenation monitor for various elective surgeries involving cardiopulmonary bypass, the output did not accurately match the values produced by an invasive intra-jugular blood saturation sensor.[9] Since the invasive sensor was also optically assessing hemoglobin saturation of blood from throughout the cerebral volume, the investigators concluded that the inaccuracy of the cerebral monitor had to do with measuring a small area of surface vessel saturation. The error was not constant but varied in a systematic way from negative to a positive bias as percent saturation varied from low to high.

The results of the referenced study emphasize the point made earlier in the sensor requirements section that any proposed sensor must monitor a diagnostically useful aspect of oxygenation. Sensors that are limited to small sampling volumes, primarily of surface tissues, will be least able to produce an oxygenation measure with dependable correlation to serious hypoxia under highly variable field conditions.

2.4.3 Cutaneous Oximeters - Cutaneous oximeters employ a Clark type electrode for polarographic detection and quantitation of oxygen tension.[10] The sensor head containing the electrode is fixed against the skin and responds to oxygen diffusing away from capillaries to the outer surface of the skin. The electrode cell contacts the skin through a permselective membrane that passes oxygen but otherwise maintains constant conditions in the cell. At a characteristic polarizing potential an electrical current passes in the sensor head that is proportional to the partial pressure of oxygen against the membrane. The state of tissue oxygenation or hypoxemia is inferred from the PO_2 value registered by the sensor.

Based on literature reports and discussion with a respiratory department equipment specialist at Florida Hospital (Orlando, FL) the cutaneous oxygen monitors have characteristics that do not recommend them for the current purpose. Fundamentally, they rely on a transport mechanism that imposes a relatively long time constant on the system. A product specification sheet for one commercial instrument quoted a 25 sec response time to indicate 90% of an imposed step change in PO_2. The thicker skin of adults can result in even longer response times or difficulty in registering detectable levels at all. On the other hand, burns to the skin have been noted when the sensor is left attached since the sensor head is heated to a temperature slightly above body temperature (42 to 48°C).

The accuracy of the cutaneous oxygen sensing electrode systems depends on transport properties of the skin and the sensor membrane. Differences in the transport property between individuals requires that the sensor response be calibrated against an independent direct measure of blood gas tension taken on that individual. In addition, the sensor systems themselves require calibration against gas standards and the membranes must be replaced as often as weekly. Care must also be exercised in making a good connection to the skin to isolate the sensing system from the ambient atmosphere. Together these issues are not severe constraints in a well equipped medical facility with sedentary subjects but they would be in the battlefield environment where low maintenance, stand alone operation is the goal.

The electrochemical cutaneous oxygen monitors do not seem suited for adaptation to a field version. A slow response to underlying change in oxygen tension would remain a critical weakness even in the absence of any other technical difficulties.

2.4.4 Photoacoustic Spectroscopy Method - Photoacoustic spectroscopy was identified as an approach early in Phase I that might be compatible with laser doppler blood flow measurements. Both methods depend on laser irradiation of the sample to generate a signal. The photoacoustic response originates by localized absorption of NIR photons that causes rapid thermal expansion generating an acoustic wave that propagates into the adjacent medium. The acoustic wave is typically detected with a microphone. Since muscle tissue exhibits characteristic NIR absorbance from Hb and Mb that indicates oxygen saturation the approach of acoustic detection of the absorption was suggested.

The apparent convenience of acoustically detecting the absorption cannot be achieved in deep tissues. The same problem faced when making direct absorption measurements in tissue makes the photoacoustic approach fail. The highly scattering nature of tissue effectively diffuses a NIR beam as it penetrates the tissue. Equation 1 expresses the relation between an acoustic pressure pulse, P_s, that develops in proportion to the incident NIR pulse intensity I_{NIR}, and the width w of the beam at the point of absorption. The term k is a collection of material property terms; for water at body temperature which is used to approximate tissue k has the value of 3.7 x 10^{-7} giving P_s in units of bar. For an incident beam on the order of a few tenths of a cm at the surface the width will grow to about 3 cm at a penetration depth of 5 cm due to the scattering. Application of equation 1 shows that incident powers of roughly 10^4 W would be required to generate an acoustic pulse of 0.001 bar, which is detectable. This level of incident power which is initially directed on a much smaller area would destroy tissue and not propagate into the deeper regions.[11]

$$P_s = k\, I\, w^{-3} \qquad (1)$$

2.4.5 Nuclear Magnetic Resonance Methods - Proton (^1H) NMR offers a means for *in vivo*, noninvasive detection of the state of oxygenation of intracellular myoglobin (Mb),[3,12,13] which is a more direct indicator of tissue oxygenation than determinations based on blood saturation (hemoglobin). However, the instrumental constraints of size and complexity preclude the NMR method from adaptability to a personal, field rugged, oxygenation sensor.

The basis of the NMR method is summarized here since this method does measure the desired parameter and thus could have very definite value for verifying the performance of another sensor system. From our assessment of methods, it appears that light absorption measurements in the visible and NIR hold the most promise for a noninvasive measurement method. However, the following discussion of some results from the NMR studies suggests once again how NIR measurements can be complicated by uncertainties in the sampled path length.

Myoglobin, a heme containing protein found in muscle tissue, is a key link in the transport and storage of intracellular oxygen. In studies to establish a more direct measure of muscle tissue oxygenation, researchers have identified ^1H NMR resonances from *in vivo* experiments that are unique for both oxy- and deoxy- forms of myoglobin. In the case of the deoxy form, Mb, the resonance peak disappears from the spectrum as O_2 is bound to give Mb-O_2; the same is true for the distinct resonance peak for Mb-O_2. The unique Mb-O_2 peak at -2.76 ppm referenced to the water peak was assigned to the methyl group on a valine residue (Val-E11).[3] The Mb resonance at +80.3 ppm relative to water results from the proximal histidyl-NH groups (His-F8) which can be resolved from the same groups on Hb.[12] The reports specify different excitation conditions for exciting the resonances so it should not be taken that simultaneous detection of Mb and Mb-O_2 is possible in a single NMR experiment.

Although ^1H NMR is now demonstrated to be a laboratory method that directly assesses the oxygen binding state of myoglobin the method does not hold near term promise for the desired sensor system. Severe limitations are posed by three aspects of the measurement. The instrumentation is large, requiring a high field strength, and extremely homogeneous magnetic

field in a configuration that surrounds the subject. Maintenance of a stable magnetic field requires a carefully controlled, constant environment. The third constraint arises from a need to accumulate signal over a period of several minutes to achieve acceptable signal to noise ratio. This signal generation time is not compatible with the response time required by the mission. The ability to determine the oxygenation state of intracellular myoglobin by ^1H NMR remains a powerful tool to consider in development of indirect methods such as NIR absorbance.

2.4.6 NIR Detection of Cellular Oxygenation - Results from one of the referenced studies that used ^1H NMR to detect the presence of deoxymyoglobin has relevant NIR sensor results also.[3] In conjunction with the NMR measurements a noninvasive NIR spectrometer was used to monitor oxygenation by changes in the diffuse backscatter at the characteristic wavelengths of Hb and Mb absorptions (they used 670 nm and 850 nm). The observation of muscle tissue at these wavelengths results in absorbance losses that could have contributions from both Hb and Mb. The independent measure of Mb/Mb-O_2 by NMR afforded the possibility to assess the relative contribution to the NIR absorption.

In a test subject group that included age matched healthy and heart failure subjects, all members exhibited Mb (i.e. tissue deoxygenation) peaks in the NMR spectrum under ischemic conditions. However, under an exercise protocol that caused sensed deoxygenation by the NIR method in the entire test population, some but not all subjects exhibited some degree of myoglobin deoxygenation. In the case of blood deoxygenation, but no Mb desaturation, the NIR measurement can be attributed to the variance due to Hb alone. That conclusion is based on the following. The relative zero point of deoxygenation was set by the NIR signal levels (for both Mb and Hb) recorded under induced ischemia. This level is very similar to the state of full Mb-O_2 saturation and Hb desaturation so the investigators concluded that the Mb/Mb-O_2 system must not contribute significantly to the NIR absorbance. However, this conclusion assumes the NIR and reference NMR method are sampling the same volume. This could very likely be a source of error based on the spacing between source and detector fiber optics. The near surface tissues, which would be rich in blood but lacking in myoglobin, would tend to dominate the signal when no means of depth discrimination was used.

The problem of variable photon path length due to scattering phenomena encountered when making NIR measurements on tissue has been described in the literature.[14] Wilson points out that if the diffusively reflected or transmitted signal is spatially or temporally resolved then the penetration depth can be established.[15] Of course as penetration depth increases the probability of photon absorption increases and the solid angle for remission increases so the detectable signal falling in the field of view of small detectors on the surface goes down. Practical sensors require a certain detectable threshold to operate and maintain immunity from noise thus there is expected to be a compromise between signal value and practical detectability that must be worked out.

Time resolved measurements of diffuse reflectance from tissue samples have been demonstrated in research laboratories.[4,16] The measurement involves picosecond pulsed laser sources and time gated detection of the returned signal with required resolution on the order of 100 ps or better. These measurements are becoming increasingly feasible with advances in

sources and detectors but are still not practical outside the laboratory particularly for thick samples. The short light pulses limit the total energy throughput because power levels cannot be raised above a safe threshold for living tissue.

Spatial resolution of the diffuse reflectance can be accomplished by changing the separation between the source of incident photons and the detector source. As the detector moves away from the source an increasing fraction of the detected signal is made up of the photons that have penetrated below the surface layers. There still remains the problem of collecting enough signal intensity to exceed the detection threshold of the detector. This problem should be addressable with existing technology though. Experiments by Jobsis[5] demonstrated that both *in vivo* cat brain and dog heart could be transilluminated; other investigators have followed up demonstrating deep penetration of muscle tissue of human limbs.[14]

2.4.7 Conclusions on Available Oximeter Approaches - The assessment of available noninvasive oximeter systems finds that no device exists for the true measurement of tissue oxygenation. The instruments measure to a different degree of precision various aspects of microcirculatory oxygen levels and assume that these reflect the oxygenation status of cells in the tissue. This proposition can be uncertain as discussed for the cerebral oximeter and generally measurements on large muscle masses have not been undertaken.

Laboratory measurements including NMR and path length resolved NIR absorbance have advanced to where tissue oxygenation information is collected. The NMR methods are inherently limited to large instruments and strong magnetic fields that are not compatible with a small sensor concept. NIR spectroscopic measurements would appear to have the best potential for a practical sensor. However, the approach must be developed in a manner that emphasizes signal processing to extract information about deep muscle tissue. The assessment of existing methods led to identification of an approach that has the potential for development into a deep tissue sensing method that can be implemented in a small device concept to meet the overall purpose of this effort. The basis of this approach is explained in the next section.

3.0 SENSOR APPROACH

3.1 Sensor Approach Selection - The first major objective of the program was met with the assessment of available methods for noninvasive determination of oxygenation. Results of this assessment were presented in the previous section. This assessment was not intended as an end in itself but a step toward identifying technology that could meet the Army concept for the sensor system as described in earlier sections. It was concluded that none of the existing instrumental approaches are amenable to direct miniaturization and hardening to give the desired sensor. However, an approach did emerge from the assessment process that appears to have an overall fit to the objectives of this program. The approach is based on a system for NIR imaging of tissue. The approach is developed in more detail in this section. Results of a numerical experiment are discussed to illustrate how sensor data would be processed to yield tissue oxygenation information. The section concludes with recommendations for pursuing the concept to a demonstration in a Phase II program.

3.2 Diffusive Tomography Approach - The problem faced in making spectral measurements on large or thick tissue samples, either *in vitro* or *in vivo*, is the highly scattering nature of the tissue. Those photons that penetrate deeply and survive to emerge are scattered over a larger area reducing their chance of collection in a detector with fixed field of view. Discriminating between photons scattered from different depths can be addressed through time discrimination, spatial resolution or a combination of these. Time resolution of returned pulses is the approach used to measure range of a scattering body from a probe source (i.e. lidar techniques). For measurements on the human body where variation in light path will be small time gating methods require ultrafast pulsed sources and corresponding fast detectors. The appropriate systems are research lab devices for now and the near future. However, a measurement based on spatial resolution of diffuse reflectance offers a means to extract deep tissue information with more practical light sources and detectors.

A general method is described in the literature for using diffusely scattered light emerging from a turbid body to generate an image of internal structure.[17] The method is directed to the application of using NIR light to image tissue structures. Muscle masses represent a significant structure within the cross section of a human limb. These same muscle tissues contain intracellular myoglobin as well as circulating hemoglobin within the small vessel/capillary network. Both of these oxygen carrying species absorb light over the red and NIR spectral region. Thus if one could image the entire muscle cross section at a wavelength that also responds to oxygenation status, the images of oxygenated and deoxygenated muscle would exhibit intensity variations proportional to the differences in oxygenation.

The imaging process depends on detection of diffusely reflected light emerging at the surface by an array of detectors that have a known spatial relation to the light source. By effectively scanning the source across the surface a series of intensity profiles are built up that depend on the specific scattering and absorptive nature of the media. Constructing the image involves iteratively matching a computer generated simulation of diffuse reflectance intensity to the measured intensity profile. Presumably a unique solution exists yielding the accurate representation of anatomical features. The required computational power depends on the degree of image resolution desired. Fortunately, the muscle masses represent large structures relative to the total cross section and they lie over the more highly opaque bone structures that will strongly suppress emergent flux at certain angles.

3.3 Diffusive Tomography Simulation For Detection of Deep Tissue Oxygenation - The method for image reconstruction is based on the approach of Singer and Grünbuam.[17] When image generation is the primary objective, as in the case of a pure tomography application, light absorption by the medium can be an interference that reduces image clarity. For the oxygenation application the interest is in the changes in absorptive properties of the tissue as a measure of oxygenation and high resolution image quality is of lesser concern. A numerical simulation experiment was run that shows that the image reconstruction method using generated diffuse remittance intensity levels provides output that reflects oxygenation differences when absorption coefficients were varied slightly. A simplified method of identifying the solution to the matrix inversion procedure was demonstrated for the type of data expected for the application. The simulations that were run are described here to illustrate how the method would work.

The sensor configuration can be envisioned as a cuff or band that encircles the arm for example. The cuff carries a series of light source-detector pairs as depicted in figure 2. It is presumed that the sources provide adequate intensity to result in measurable remittance intensity at some or all of the detector sites. Furthermore, the sources operate at a wavelength in the NIR where hemoglobin and myoglobin each show different absorptivity in their respective oxy and deoxy forms. The measurement process involves determining the light intensity arriving at every detector as each of the sources is lit in sequence. The coherent image quality is destroyed by the high degree of scattering but the emitted intensity profile develops as a result of all scattering and absorption events that occur as photons travel through the heterogeneous medium. The forward process of light propagation in the tissue is represented by radiation transport models for turbid, diffusive media.[11,18,19]

The diffusive tomography technique is based on inverting the radiation transport model for light diffusion in scattering media. A simplified model of light diffusion in tissue serves to illustrate the technique. The tissue is divided into regions called voxels. A single voxel element is depicted in figure 3. Light of intensity, I, launched from a source on the surface, enters the ij^{th} voxel where a fraction, v_{ij}, is absorbed. Light that is unabsorbed ($I = 1-v_{ij}$), gets elastically scattered into an adjacent voxel. A fraction, f_{ij}, is scattered forward into the next voxel, another fraction, s_{ij}, is scattered to the side (only left and right side scattering is illustrated in figure 2) into adjacent voxels, and the amount, b_{ij}, is scattered backward.

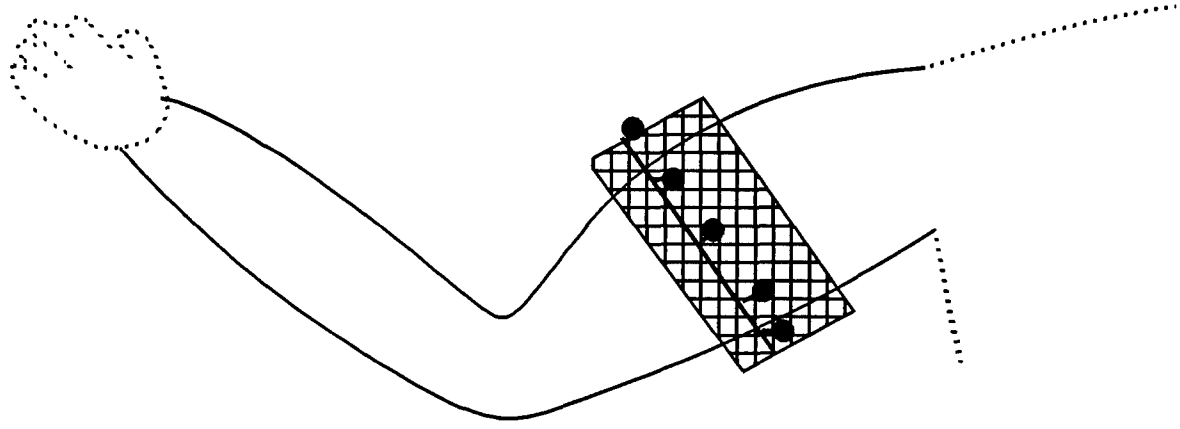

Figure 2. A sketch of the sensor device concept showing a cuff with multiple sources and detectors.

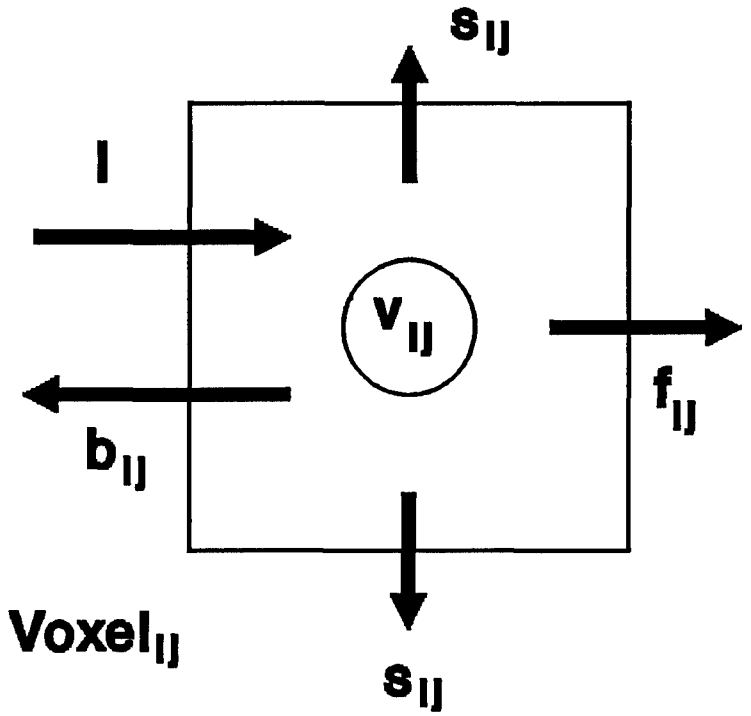

Figure 3. The voxel element is used to model diffusion of light in media that exhibits anisotropic scattering and absorption.

For the simulation a two dimensional model was constructed. The image in figure 4 shows how a grid of voxels might be laid out for a cross section of the upper arm and how light (arrows) might propagate from a source to multiple detectors due to scattering. (Note: the cross sectional image of the arm is modeled after an image downloaded from the Visible Human Project). The exact geometry of the grid is not critical. The inversion algorithm outlined below depends only on the existence of multiple source-detector pairs and not on the exact geometry. The geometry would be taken account of through an initial calibration performed for a given system of sources and detectors.

Let $V = [v_{ij}]$ be the M by M array of voxel absorption values. The arrays of forward, side and back scatter coefficients, F, S, and B are similarly defined. With the absorption and scattering probabilities for each voxel described by the arrays V, F, S, and B, let $T = [t_{ij}]$ be the N by N array of source-detector propagation losses as described for V above.

In operation, the values that define the matrix T would be measured as the output of detectors in response to the source inputs. Algorithms are then needed to invert the measured T to give estimates of V, F, S, and B. Variable states of tissue oxygenation will result in changes mainly in the V values, so that F, S, and B can be considered to be constant. Also the changes in the V values, δV, due to oxygen changes will also tend to be small. These two considerations make the inversion algorithm for the oxygenation application simpler than that discussed by Singer.[17] For the deep tissue oxygen application, only the absorption, v_{ij}, values are needed since they will be used to infer the state of oxygenation of hemoglobin and myoglobin. For this simulation a simplified linearized inversion technique was developed.

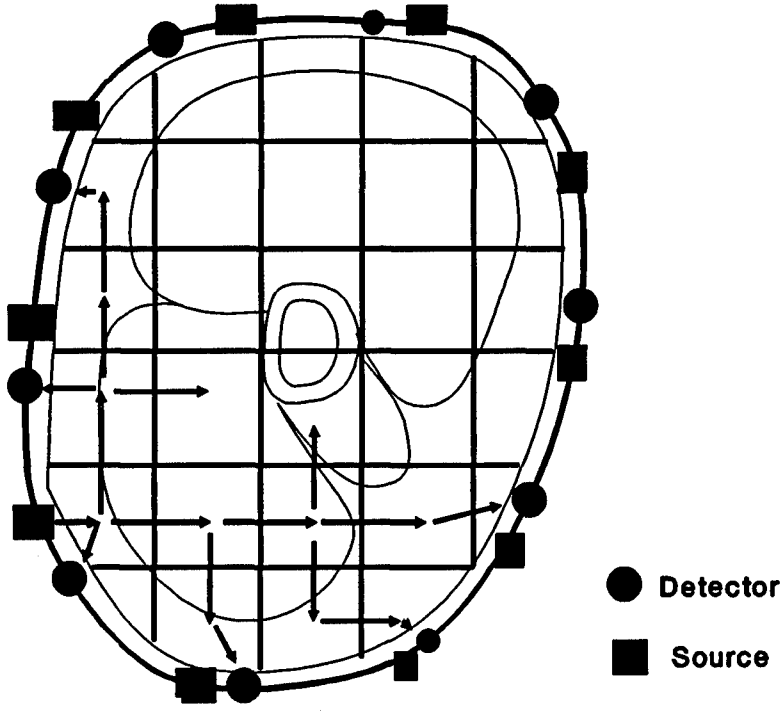

Figure 4. A schematic cross sectional representation of a sensor cuff on the arm. Arrows suggest photon pathways in a coarse voxel grid.

A numerical experiment was conducted to verify the practicality of the diffuse tomographic approach for deep tissue oxygenation measurements. The values of T (remitted intensity levels) were simulated using a Monte Carlo numerical algorithm. The matrix T was then inverted to find δV, the difference in absorption associated with specific voxels, for test cases that reasonably simulate the tissue case. The algorithm was also exercised using random noise at input to verify that δV and hence oxygenation could be detected in the presence of noise.

To test the method propagation values were calculated for a 2 by 2 voxel grid using values $F = 0.65$, $S = 0.15$, and $B = 0.05$, based on reported tissue measurements.[19,20,21]. The matrix V_0 was initialized to the transmission values:

$$Vorig = \begin{bmatrix} 0.4 & 0.4 & 0.4 & 0.4 \\ 0.4 & 0.2 & 0.2 & 0.4 \\ 0.4 & 0.2 & 0.2 & 0.4 \\ 0.4 & 0.4 & 0.4 & 0.4 \end{bmatrix}$$

The surface plot in figure 5 shows the values of propagation loss, T, between pairs of sources and detectors. The location of light sources going clockwise around the grid is the right-left axis, and similarly the detector location clockwise around the grid is the front-back axis; the common starting point is at the right hand front corner of the plot so the location index increments up going right to left and front to back. The signal received (i.e. diffusely emitted light) is represented on the vertical axis. The strongest signals are for source-detector pairs at nearly the same location corresponding to backscatter from the tissue. The model thus agrees with intuition and with qualitative observations.

A matrix D, which simulates a change in absorption at specific sites corresponding to altered oxygenation, was calculated by perturbing V at some of the sixteen matrix locations and calculating a new value for $T = T_0 + \delta T$. The perturbation, δV, to the absorption values is represented by dV_{orig}. When the matrix representing the altered transmission levels is inverted, the resulting estimate for δV is given by dV_{est}:

$$dVorig = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0.1 & 0.1 & 0 \\ 0 & -0.1 & -0.1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \qquad dVest = \begin{bmatrix} 0.004 & 0.001 & 0.002 & 0.004 \\ -0.004 & 0.106 & 0.085 & -0.002 \\ 0.002 & -0.063 & -0.042 & 0.004 \\ 0 & 0 & 0.001 & -0.003 \end{bmatrix}$$

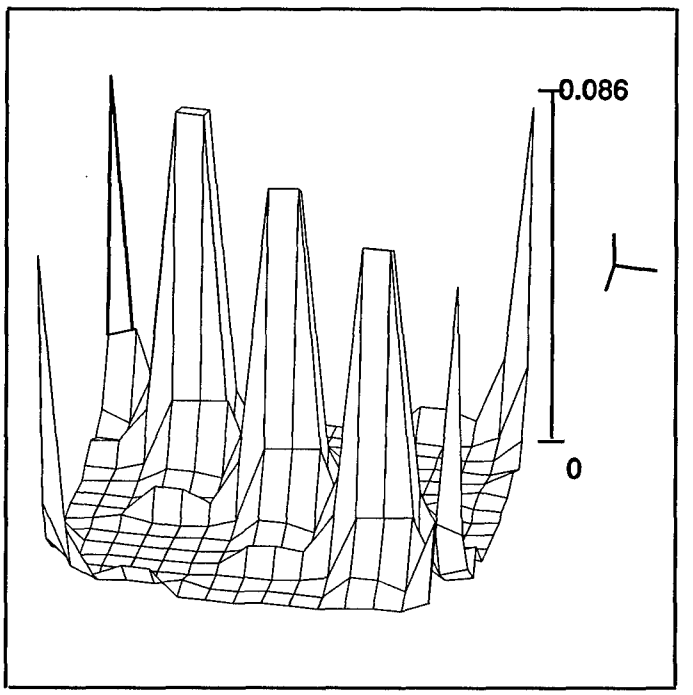

Figure 5. The surface plot shows simulated light propagation through a tissue model. The x-y plane shows source and detector location; the magnitude of the transmitted intensity is on the vertical axis.

The agreement between dV_{est} and dV_{orig} represents the ability to use detected changes in the spatial profile of surface remittance intensity to deduce in-depth changes in absorption. The degree of agreement illustrated in this evaluation case indicates the potential applicability of the method for tissue oxygenation measurements. Even better agreement might be expected with an optimized algorithm.

The simulation was also run to test for sensitivity to noise, which will be a very real part of any light measurement process. Random noise levels corresponding to 10% of T were input to the inversion algorithm with the following result:

$$dVnoise = \begin{bmatrix} -0.004 & -0.001 & 0.001 & 0.002 \\ -0.002 & 0.029 & -0.022 & -0.002 \\ 0 & -0.012 & 0.012 & 0.001 \\ -0.003 & 0.002 & -0.001 & -0.002 \end{bmatrix}$$

The apparent changes in absorption due to the imposed noise, dV_{noise}, are random and all are significantly smaller than the estimate for the deterministic test case dV_{est}. This demonstrates that the linearized inversion algorithm can reject noise. The larger values in the center of the region seem to be a reflection of greater absorption associated with deep penetration of light into tissue.

The model calculations discussed above indicate that the diffuse reflectance tomography approach has the potential to be exploited for detection of deep tissue oxygenation.

3.4 Sensor Device Concept - Figure 2 shows a schematic representation of an envisioned sensor array for imaging a cross section of the arm. A series of source emitters and detectors are incorporated into a band that goes around the limb. The emitters, selected for an appropriate wavelength, would be lit sequentially to effect a scan. The intensity at all detector nodes would be registered for each emitter location to generate the intensity profile used for image reconstruction. Changes in oxygenation would show up as different image intensities originating from the same structural features. The information might best be represented as a difference image generated by subtracting one image from another in a way that would then highlight only areas that changed.

The sources and detectors that make up the device are expected to be based on semiconductor technology including light emitting diodes, laser diodes and diode detectors. These sources are available at appropriate wavelengths to match the hemoglobin/myoglobin absorbance bands.

3.5 Sensor Device Development - The next stage in developing the diffuse tomography approach would be to fabricate a laboratory prototype device and verify that useful data can be generated with light sources that are practical for a compact system. An experimental platform for conducting the developmental work is straightforward and readily assembled for timely

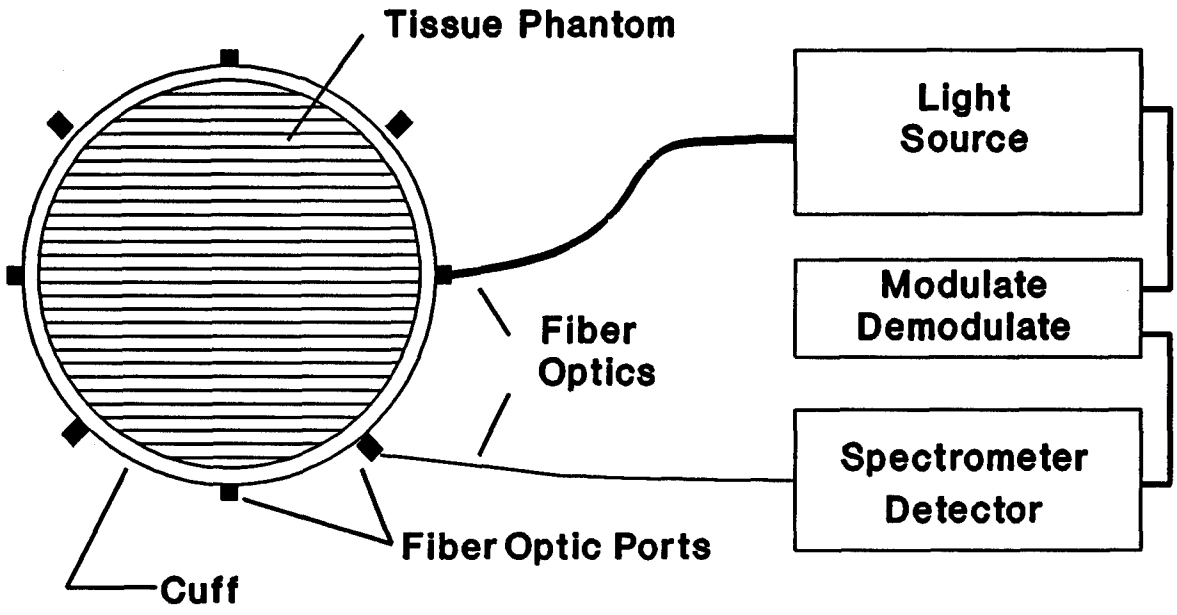

Figure 6. The system for breadboard development and testing of the sensor.

pursuit of feasibility. Two basic elements are involved: a tissue phantom and a spectral analysis system. These elements are represented in the generic system shown in figure 6. The tissue phantom simulates the scattering and absorption characteristics of living, whole body tissue. The spectral analysis system allows light of different wavelengths to be directed into the phantom and analyzed for spatial distribution and intensity as it is scattered back out of the scattering/absorbing medium.

Experimental development would identify the optimal NIR wavelength or wavelengths for observation of absorption changes. A major objective would be to identify the necessary source power levels needed to generate usable output intensity for image generation. This process would involve determining the number and position of the required multiple sources and detectors together with the power levels. As these parameters are established appropriate sources could be identified for design into a laboratory prototype demonstrator device. The incorporation of sources and detectors into the test apparatus is represented in figure 7 and makes use of the same tissue phantom used in the first level test and development device.

In conjunction with development of the hardware elements for the sensor an effort would be required to optimize the image reconstruction algorithm. The preliminary work done under the Phase I program suggests that a relatively simple approach will be successful since changes in the scattered light intensity profile will not exhibit complex structure.

The program required to get to a laboratory prototype feasibility demonstration is estimated to take about two years at a 2 to three man level of effort.

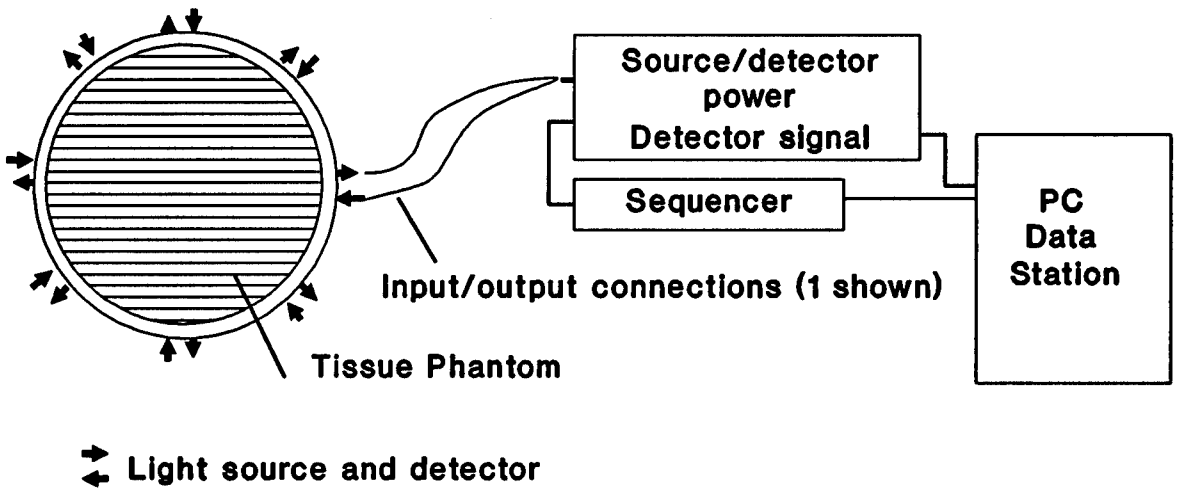

Figure 7. The laboratory prototype sensor features a multiple source-detector arrangement to profile the diffuse reflectance.

4.0 SUMMARY AND CONCLUSIONS

The program conducted under the Phase I period carefully identified and defined the problem of noninvasive sensing of deep tissue oxygenation. Existing technology was assessed in light of the requirements needed to meet the Army objectives for a sensor system that integrates into a much larger effort to equip the foot soldier of the future with advanced protective capabilities. An approach based on diffuse reflectance tomographic imaging was identified as having the potential to meet the objectives of the sensor development initiative being sponsored by the U.S. Army.

Diffusive tomography in the context of this application would generate an image of the absorption characteristics of the target tissue mass, skeletal muscle as the initial focus. When the imaging wavelength is matched to the absorption of hemoglobin and myoglobin the resulting image would reflect the state of oxygenation in that tissue. As changes were to take place in the degree of oxygenation the resulting absorption image would change accordingly. The power of the method is the ability to process the detected light signal to determine the spatial origin thus surface and deep tissue information can potentially be resolved. While there is mention of this approach in the literature there are no reports of development into a practical sensor system.

The research and development program for carrying this approach forward to a laboratory prototype demonstration was set forth in a proposal to the U.S. Army Medical Research and Materiel Command for Phase II support.

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